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Vitamin K in sport activities: a less considered benefit for athletic training

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Abstract

Vitamin K is a family of different fat-soluble molecular compounds, represented by a single form synthesized by plants (vitamin K1), and multiple forms synthesized by bacteria (vitamins K2). Several vitamin K-dependent proteins are synthesized based on vitamin K co-enzymatic activity. The sources of vitamin K are mainly green and leafy vegetables, fruits, herbs, green and herbal teas and plant oils - for vitamin K1 and fermented animal foods - for vitamin K2.

Vitamin K and its dependent proteins have important roles in several physiological or tumoral processes: bone mineralization, blood clotting, metabolism of blood vessel walls, tumoral angiogenesis and even cell growth and nervous system biochemistry (aspects of behavior and cognition). Vitamin K deficiency is associated with several diseases, including osteoporosis, vascular calcification and even depression.

Through its involvement in cardiovascular and nervous system function, and bone metabolism, vitamin K supplementation could improve exercise capacity.

Keywords: vitamin K1, vitamin K2, diet, exercise capacity.

Biochemistry and metabolism of vitamin K

Vitamin K is known as a fat-soluble compound which has a common 2-methyl-1,4-naphthoquinone nucleus but differs in the structure of a side chain of the third position and is essential in the post-translational modification of a set of proteins which are called vitamin K-dependent proteins (Shearer & Newman, 2014). The discovery of vitamin K is related to different experiments which investigated the role of cholesterol in the diet of chicks – a curative factor present in vegetable and animal sources was a new fat-soluble vitamin, which was called vitamin K (Gröber et al., 2014). Phylloquinone is known as vitamin K_1 and has a phytyl side chain, menaquinones are known as vitamin K_2, and the synthetic compounds are named menadione and menadiol (Braasch-Turi & Crans, 2020). The natural nutritional sources of vitamin K1 are represented by fruits (e.g., avocado, kiwi, and green grapes), seeds, green and leafy vegetables (e.g., kale, Brussels sprouts, broccoli), herbs (e.g., cilantro, parsley), plant oils (soybean oil, canola, and olive oils), and the sources of vitamin K_2 are represented by bacterial fermented foods (fermented butter or cheese, curdled cheese), or foods of animal origin (egg yolk, foie gras, beef liver, poultry products) (Elder et al., 2009). We obtain by nutrition mostly vitamin K1 (phylloquinone), and intestinal bacteria synthesize K2 *de novo* and also convert vitamin K1 to vitamin K2 (menaquinones) (Kiela & Ghishan, 2016). The absorption of vitamin K depends on its incorporation into mixed micelles in the intestinal lumen. This process requires the presence of bile acids and the products of pancreatic enzymes (Iqbal & Hussain, 2009). Dietary vitamin K is absorbed in the proximal small intestine by active transport; then vitamin K is incorporated into chylomicrons which are then secreted into the lymph and pass into the blood (Kiela & Ghishan, 2016). Extrahepatic tissues use vitamin K_1 to synthesize menaquinone-4, from chylomicrons and

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very-low-density lipoproteins. Menaquinones are absorbed from the terminal ileum, and menadione is absorbed by way of the portal system and some of this compound is absorbed into the lymphatic system (Kulkarni, 2012). On the other hand, menadione is metabolized very fast and only a small proportion is converted to biologically active menaquinone-4. Because of the low levels of transporting lipoproteins, the transport of phylloquinone from maternal to fetal circulation is poor (Schurgers & Vermeer, 2002).

One of the most important metabolic functions of vitamin K is being a coenzyme in the carboxylation of protein-bound glutamate residues to yield gamma-carboxyglutamate residues. Vitamin K-dependent proteins refer to several proteins, especially the Gla proteins, and the enzymatic reaction is catalyzed by gamma-glutamyl or vitamin K-dependent carboxylase which is linked to a cyclic salvage pathway – the vitamin K epoxide cycle (Card et al., 2014).

The physiological roles of vitamin K

The role of vitamin K is very important and there are many vitamin K-dependent proteins that are found in bone tissues such as osteocalcin, matrix Gla protein also identified as MGP, Gas6 and protein S (1). The most important processes involving vitamin K are: blood-clotting, bone mineralization and density, cell growth, metabolism of blood vessel walls (Volpe, 2016), and even nervous system biochemistry (Bourre, 2006).

Table I
Vitamin K in human metabolism - activity and function (modified after Kulkarni, 2012).

Activity	Function
Blood clotting	Carboxylation of coagulation factors II, VII, IX, X
Bone metabolism	Carboxylation of osteocalcin Decreases urinary calcium excretion
Atherosclerosis	Carboxylation of matrix Gla protein
Nerve signaling	Carboxylation of growth arrest-specific protein
Kidney stones	Carboxylation of nephrocalcin

Vitamin K-dependent proteins

Many vitamin K-dependent proteins need gamma carboxylation to exercise their physiological activity. Vitamin K exerts its physiological activity by acting as a cofactor in the process of gamma carboxylation of its different dependent proteins (El Asmar et al., 2014; Schlieper et al., 2016).

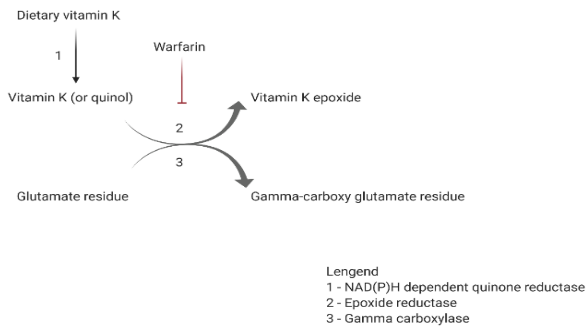

Fig. 1 – Vitamin K – mechanism of action.
Legend: 1 – NAD(P)H-dependent quinone reductase; 2 – Epoxide reductase; 3 – Gamma carboxylase.

According to Fig. 1, dietary vitamin K is transformed into quinol by NAD(P)H-dependent quinone reductase. The obtained compound is then utilized by a gamma-carboxylase to modify glutamate residue into gamma-carboxyglutamate residue in all vitamin K-dependent proteins, and the active form results. Vitamin K-dependent proteins such as the clotting factors II, VII, IX and X are gamma-carboxylated in the liver to obtain an active form; anticoagulant factors (protein C, protein S and protein Z) are gamma-carboxylated mostly in the liver and in extrahepatic tissues. Other well-known vitamin K-dependent proteins are represented by osteocalcin and matrix Gla protein. Carboxylation reaction is linked to the oxidation of vitamin K and obtaining vitamin K epoxide which is recycled back to the reduced form by epoxide reductase. Warfarin inhibits epoxide reductase and vitamin K stores are diminished, and the production of coagulation factors is inhibited (El Asmar et al., 2014; Danziger, 2008).

Two vitamin K-dependent proteins, Gas6, and to a lesser extent, protein S, are actively involved in the nervous system function. Gas6 is involved in neuron and glial cell mitogenesis, chemotaxis, growth and survival, playing key roles in the nervous system (Ferland, 2012). Protein S protects the brain through its antithrombotic and neuroprotective actions: in the brain of mice lacking protein S, severe thrombosis and necrosis were observed (Saller et al., 2009).

Gla proteins are present in the bone matrix and are named Gla proteins because their molecules contain gamma-carboxyglutamic acid. The most common Gla proteins are osteocalcin and matrix Gla protein.

Studies have indicated that osteocalcin is not the only protein present in bone, and substantial amounts of non-osteocalcin Gla were found in cartilage. Another protein capable of self-associating in solution was named matrix Gla protein, a single-chain polypeptide that contains five Gla residues at position 2, 37, 41, 48 and 52 of the 79 amino acid residues of human and bovine protein, which are stabilized by one intra-chain disulfide bond (Bjørklund et al., 2020).

Matrix Gla protein is a vitamin K-dependent and gamma-carboxyglutamic acid-containing protein and also a non-collagenous extracellular matrix protein. MGP contains post-translationally modified gamma-carboxyglutamic acid residue resulting from vitamin K-dependent carboxylation. This protein was first isolated and sequenced from bovine bone and cartilage, but in humans it is also found in tissues such as the lung, kidney, heart or others. Compared to osteocalcin, matrix Gla protein is more widely distributed in the body (Price, 1989; Yagami et al., 1999).

Using different techniques such as direct sequencing or cloning, many structures of matrix Gla protein are available. Even if matrix Gla protein was first isolated from bone, it has been shown to be expressed in different tissues, with a high level of expression in vascular smooth muscle cells, and the metabolic role of matrix Gla protein is very difficult to be clarified. Many experiments were conducted on mice, some of them informing about the development of spontaneous calcification of arteries (Wen et al., 2018; Lomashvili et al., 2011). Mutation in the MGP gene was associated with a rare human autosomal recessive condition named Keutel syndrome, which is characterized by midface hypoplasia and ectopic abnormal calcification (Munroe et al., 1999).

Vascular calcification is a passive event that occurs in the absence of functional inhibitors and it is also possible to demonstrate calcification of the elastic lamellae in the arteries and heart valves in a rat model using high concentrations of warfarin and also sufficient vitamin K to prevent hemorrhage. Even if the role of matrix Gla protein in preventing ectopic calcification is well established, the mechanisms that are involved in this response are less known. There are some possible roles of matrix Gla protein that can be summarized, such as binding calcium ions in the form of crystals in tissues or binding and inactivating bone morphogenic protein-2 and bone morphogenic protein-4. The capacity of matrix Gla protein to bind matrix components such as vitronectin or elastin and its influence on apoptosis of vascular smooth muscle cells suggested that this protein can be involved in ectopic mineralization (Fig. 2). There are a large number of genes that are known to be involved in the mineralization process of the extracellular matrix (El Asmar et al., 2014; Danziger, 2008; Bjørklund et al., 2020; Sterzyńska et al., 2018; Epstein, 2016; Jaminon et al., 2020).

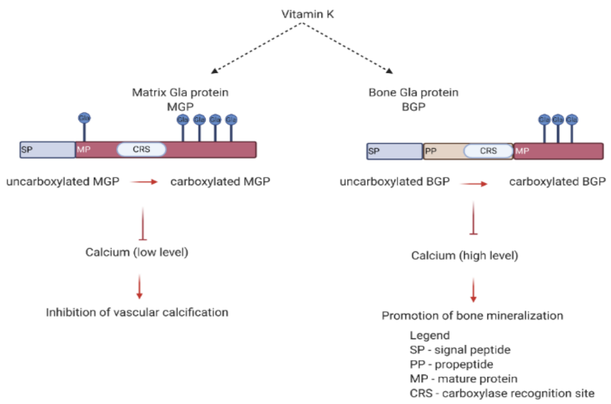

Fig. 2 – Effect of vitamin K on vascular and bone health. Structural organization of matrix Gla protein and bone Gla protein.
Legend: SP – signal peptide; PP – propeptide; MP – mature protein; CRS – carboxylase recognition site.

The physiological function of matrix Gla protein is to inhibit tissue calcification, pathological calcification or abnormal angiogenesis responsible for tumor progression. It is also known that matrix Gla protein expression is related to cellular differentiation and tumor progression, and it can be considered that matrix Gla protein expression could be tumor type dependent. Other important aspects are: a negative correlation between matrix Gla protein expression and tumor progression or metastasis in renal or prostate cancer, an up-regulation of matrix Gla protein transcript in breast cancer or glioblastomas associated with tumor progression and poor prognosis, and, the most important, the binding between matrix Gla protein and fibronectin, which enhances cell adhesion and spreads cancer cells (Sterzyńska et al., 2018; Jaminon et al., 2020; Graham & Miftahussurur, 2018).

Matrix Gla protein is also involved in lung development. Studies reported that a newly generated human MGP transgenic mouse suffers severe morphological defects in the pulmonary artery tree, considering that matrix Gla protein is involved in the development of lung vasculature and also in embryonic lung morphogenesis. Abnormal vascular development is correlated with abnormal morphology and cell differentiation in the terminal airways (Bjørklund et al., 2020; Yao et al., 2007; Pazhouhandeh et al., 2017).

Vitamin K supplementation

In adults, the average food intake of vitamin K is 122 mcg for women and 138 mcg for men daily. When both foods and supplements are considered, the average daily intake increases to 164 mcg for women and 182 mcg for men. The recommended intakes, depending on gender and age, are presented in table II (2).

Table II
Recommended intakes for vitamin K (after (3).

Age	Male	Female
Birth to 6 months	2.0 mcg	2.0 mcg
7–12 months	2.5 mcg	2.5 mcg
1–3 years	30 mcg	30 mcg
4–8 years	55 mcg	55 mcg
9–13 years	60 mcg	60 mcg
14–18 years	75 mcg	75 mcg
19+ years	120 mcg	90 mcg

In healthy people consuming a varied diet, vitamin K nutritional intake is sufficient and the clinical measures of blood coagulation will not be altered (3).

Deficiency of vitamin K can be caused by small bowel injury and malabsorption, chronic kidney disease and dialysis, and vitamin D deficiency, aging, or intake of broad-spectrum antibiotics, and this vitamin K deficiency can cause hypoprothrombinemia and hemorrhagic disorders (Kiela & Ghishan, 2016).

Several vitamin K forms can be used as dietary supplements: vitamin K1 as phylloquinone or phytonadione (a synthetic form of vitamin K1) and vitamin K2 as MK-4 (menaquinone-4) or MK-7 (menaquinone-7) (4).

Several studies showed the implication of vitamin K in chronic diseases (such as cardiovascular disease and osteoarthritis), and therefore, vitamin K deficiency can be associated with an increased risk for mobility disability, especially the disablement process in older age (Shea et al., 2020). In a study on knee osteoarthritis, a leading cause of lower extremity disability among older adults in the US, Misra et al. showed that vitamin K deficiency, even at a subclinical level, is associated with an increased risk of developing knee osteoarthritis and cartilage lesions (Misra et al., 2013). Therefore, considering its involvement in bone metabolism and mineralization (osteocalcin synthesis), vitamin K supplementation could improve the clinical condition of patients with osteoarthritis. In the case of this disease, with very limited treatment options, patients could greatly benefit from the prophylactic potential of vitamin

K supplementation, ensuring the recommended intakes for this micronutrient (Ishii et al., 2013; Thomas et al., 2018).

Vitamin K and exercise performance

The link between diet and exercise practice is clearly expressed at the bone tissue level: mechanical stimuli signal towards osteoblasts and osteoclasts, affect osteocyte function and remodel the bone architecture. The dietary modulators of bone metabolism, especially 1,25-dihydroxyvitamin D_3 and several forms of vitamin K, can improve bone health, when they act synergistically with an exercise regimen (Willems et al., 2017). Several studies, including a meta-analysis of randomized controlled trials, showed that oral supplementation with vitamin K (phytonadione and menaquinone) can reduce bone loss and prevent osteoporosis and fractures (Cockayne et al., 2006; Tamura et al., 2007; Lanham-New, 2008).

Also, important in the decision to perform constant physical exercise is the nervous system and cognition, and there is a strong relationship between vitamin K nutritional status and brain sphingolipids (neuronal membrane components). New researches highlighted important effects of vitamin K status, especially of MK-4, in the brain and other components of the nervous system, involving even aspects of behavior and cognition (Ferland, 2012). A cross-sectional analysis from a large cohort study showed that a higher dietary vitamin K intake was significantly associated with a lower presence of depressive symptoms (Bolzetta et al., 2019).

In practicing exercise, cardiovascular modifications should be taken into account. In a study on the effects of oral vitamin K2 supplementation during exercise, it was shown that an 8-week consumption was associated with increases in maximal cardiac output and heart rate, but not in stroke volume (McFarlin et al., 2017). Another study indicated that vitamin K2 supplementation for 4 weeks increased maximal cardiac output by 12% in aerobically trained male and female athletes, and also improved heart rate and lactate levels (5). Also, due to its protecting effect on arterial metabolism (through its action on matrix Gla protein) (Fusaro et al., 2020), it is possible that vitamin K nutritional status may improve exercise capacity.

Considering the involvement of vitamin K in bone and physical function, researchers have examined vitamin K status in athletes. In a study assessing the nutritional status correlated with bone metabolism in professional male baseball players, Iwamoto et al. showed that some athletes had low serum concentrations of vitamin K1, even if all athletes consumed the daily vitamin K requirements (Iwamoto et al., 2010). In female elite athletes, who use oral contraceptives or present amenorrhea induced by strenuous exercise, some bone mass can be lost rapidly, even in relatively young athletes, and low bone mass can lead to stress fractures (Braam et al., 2003). The study of Craciun et al. demonstrated that vitamin K supplementation decreases bone resorption markers and increases bone formation, improving the balance between bone formation and resorption (Crăciun et al., 1998).

Sumida et al., examining the nutritional status of Shorinji Kempo athletes (a Japanese martial art considered to be a modified version of Shaolin Kung Fu) who suffered from sports-related fractures, reported that 15 of 16 athletes had an insufficient vitamin K intake (Sumida et al., 2012). In a larger study (791 subjects) examining the correlation between vitamin K1 status and knee osteoarthritis in older athletes, Shea et al. reported that individuals with low plasma concentrations had a greater progression of knee articular cartilage damage (Shea et al., 2015).

Conclusions

1. Vitamin K and vitamin K-dependent proteins have important roles in several physiological and tumor processes: blood clotting, bone mineralization and density, cell growth and nervous system biochemistry, vascular wall development and metabolism, tumor angiogenesis, cancer cell spreading and metastasis formation.
2. Vitamin K status is related to pathological conditions such as osteoarthritis and osteoporosis.
3. More randomized controlled trials are needed to establish the pharmacological doses of vitamin K supplementation in order to ensure bone and vascular health, fracture prevention, and also to improve athletic performance.

Abbreviations

MGP: matrix Gla protein; TGF-β: transforming growth factor-β

Conflict of interests

The authors declare no conflict of interest.

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